CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074107

BIOEQUIVALENCE REVIEW(S)

JUN - 9 1992

Atenolol/Chlorthalidone
100 mg/25 mg, 50 mg/25 mg tablets
ANDA #74-107
Reviewer: James D. Henderson
File: 74107SDW.891

Sidmak Laboratories
East Hanover, NJ
Submitted:
August 22, 1991

Review of a Bioequivalence Study, Waiver Request, and Dissolution Data

The sponsor has submitted the results of a bioequivalence study comparing its test product atenolol/chlorthalidone 100/25 mg tablet (ANDA #74-107) with the reference product Tenoretic® (ICI). In addition, the sponsor has requested waiver from bioequivalence study requirements for its test product atenolol/chlorthalidone 50/25 mg tablet and submitted dissolution data for both strengths.

I. Background

Atenolol/chlorthalidone is a combination product indicated for the treatment of hypertension (but not as initial therapy), combining the additive antihypertensive effects of the ß-1 blocking agent atenolol and the diuretic chlorthalidone. About 50% of an oral dose of atenolol is absorbed with the remainder fecally excreted unchanged. Atenolol is a racemate with the (-)-enantiomer accounting for its pharmacologic activity; the renal clearance and half-life ($t_{1/2}$) of both enantiomers do not differ. Peak blood levels are reached in 2-4 hr, with the absorbed portion eliminated principally by renal excretion. The plasma $t_{1/2}$ of atenolol is about 6-7 hr. After a 50-100 mg dose, ß-blocking and antihypertensive activity both persist for 24 hr; however, the antihypertensive effect does not appear to be related to plasma levels. Chlorthalidone is about 64% available orally and about 65% of the absorbed dose is excreted in the urine. The plasma $t_{1/2}$ is about 44 hr, with a longer blood $t_{1/2}$ due to sequestration of the drug in erythrocytes.

The innovator product is Tenoretic® 100 (ICI) available as 100 mg tablets (NDA #18-760, 6/8/84) and Tenoretic® 50 (ICI Pharma) as 50 mg tablets (NDA #18-760, 6/8/84); both are rated "AB".

II. Study Site

Clinical Site: (b)4 - Confidential Business

Medical Direct
Scientific Dir

Study Dates: Protocol #900941
Period 1 - 4/20-25/91
Period 2 - 5/4-9/91

Analytical Site: (b)4 - Confidential Business
Analytical Director

Analysis Dates: 5/10-6/11/91 (atenolol)
5/22-6/5/91 (chlorthalidone)

III. Study Design

The study was a two-way crossover (two periods, treatments, and sequences), randomized, single dose study comparing the sponsor's test product atenolol/chlorthalidone 100/25 mg tablets with the reference product Tenoretic® 100 (ICI) in healthy adult males with a 14-day washout period between treatments.

IV. Subject Selection

Adult male volunteers (N=26, for completion of 24 subjects) who gave written informed consent were selected according to the following criteria:

Inclusion Criteria:

- 18-55 years old
- weight at least 60 kg and within ± 15% of ideal body weight (Table of "Desirable Weights of Adults", Metropolitan Life Insurance Company, 1983)
- healthy as judged by medical history, physical examination, and laboratory tests

Exclusion Criteria:

- history or presence of CV, pulmonary, hepatic, renal, hematological, or significant GI disease
- history or presence of bronchospastic disease, diabetes, hyperthyroidism
- alcoholism or drug abuse within the last year
- hypersensitivity or idiosyncratic reaction to either active ingredient, or to any sulfonamide-derived drug, ß-blocking agent, or monosulfamyl diuretic
- sitting blood pressure (BP) < 110/70 mm Hg at screening or 100/60 mm Hg before dosing
- abnormal diet within the four weeks preceding the study
- tobacco use in any form
- Subjects who, through study completion, would have donated more than 500 ml of blood in 14 days, 750 ml in 3 months, 1000 ml in 6 months, 1500 ml in 9 months or 2000 ml in a year.
- completion of another clinical trial within 28 days of study start

V. Study Procedure

Treatments: Subjects were admitted to the clinical study facility at least 12 hr before dosing. After an overnight fast, each subject received one of the following treatments:

1) Treatment A (test product) - atenolol/chlorthalidone 100/25 mg tablet, Sidmak Lot #90-026T; theoretical batch size not stated, finished batch size not stated; potency not stated.

2) Treatment B (reference product) - Tenoretic® 100 tablet, ICI Lot #DA-161, exp 2/94; potency not stated.

Each treatment was administered with 240 ml of water. After a 14-day washout period, each subject was crossed over to the alternative treatment.

Blood Sampling: Blood samples (10 ml) were collected into EDTA Vacutainers® at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 16, 18, 24, 36, 48, 72, 96, and 120 hr postdose. Whole blood was analyzed for both atenolol and chlorthalidone except at 1.5, 2.5, and 5 hr (atenolol only), and at 14, 16, 48, 72, 96, and 120 hr (chlorthalidone only). Blood samples were stored in aliquots at -20°.

Meals/Fluids: Subjects were fasted overnight and for 4 hr postdose. Water was prohibited for 2 hr predose and for 4 hr postdose, but allowed freely at all other times. Standard meals were provided at 4 and 9 hr postdose, and at appropriate times thereafter.

Confinement: From 12 hr predose until after the 48-hr blood draw; subjects returned for the 72-, 96-, and 120-hr blood draws.

Restrictions:

- no medication of any kind for the 14 days preceding the study
- Consumption of alcohol- or xanthine-containing beverages and foods was prohibited for 48 hr predose and during sample collection. Decaffeinated beverages were allowed after the 48-hour blood draw.
- normal activity for the first 4 hr postdose, avoiding both vigorous exertion and complete rest

Vital Signs: Sitting BP and heart rate (HR) measurements were taken predose and at 1, 2, 3, 4, 6, 8, 12, 16, and 24 hr postdose. Changes in diastolic and systolic BP and in HR were calculated by subtracting baseline values from postdose values.

VI. Analytical Methodology

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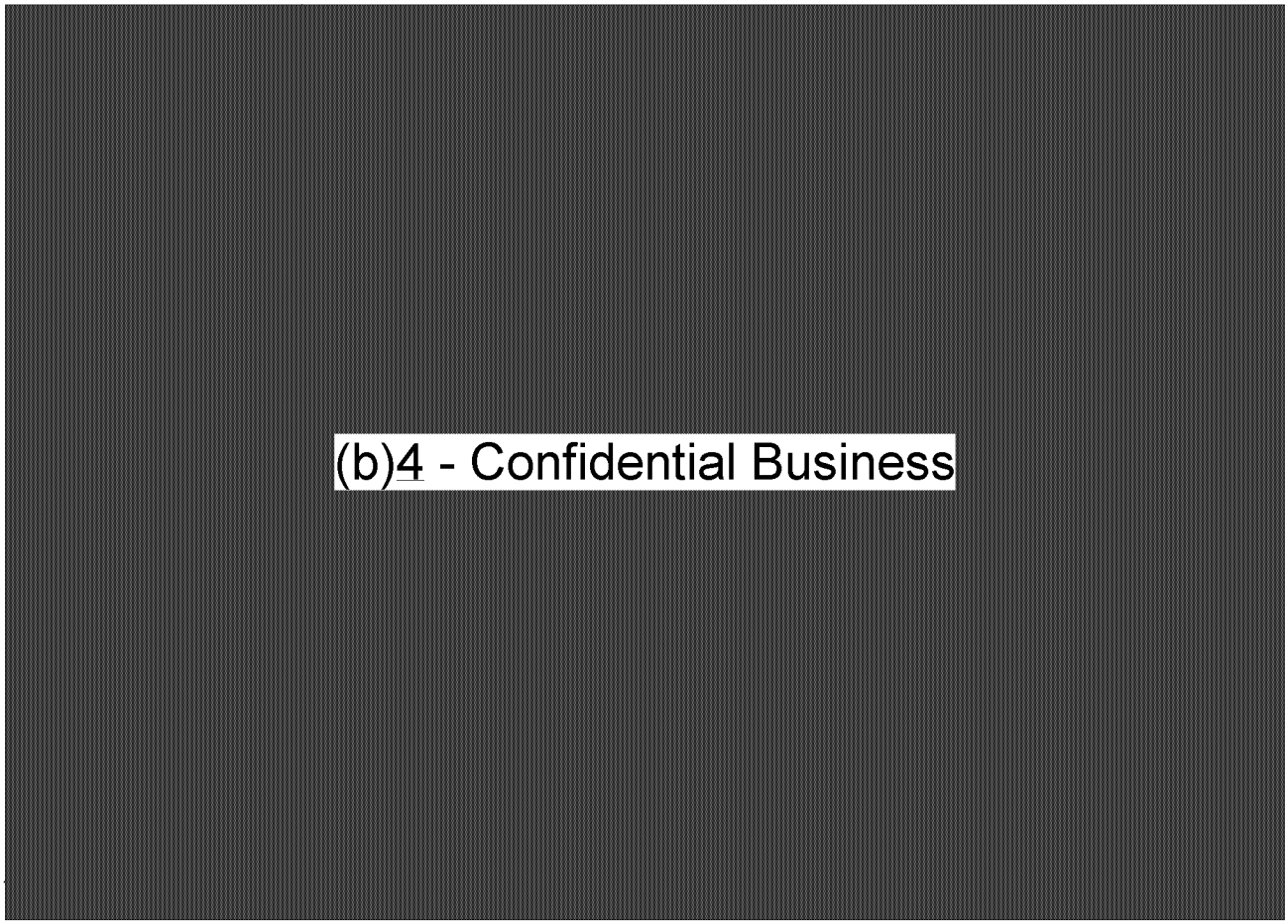


VII. Data Analysis

Data from the first 12 subjects in each dosing sequence to complete the study was analyzed by ANOVA with subjects, periods, and formulations as factors, and sequence as a between-subjects factor for the pharmacokinetic parameters: AUC, AUCINF, CMAX, TMAX, KEL, $T_{\frac{1}{2}}$, and concentration at each sampling point. AUC's were determined by the trapezoidal method, with AUCINF = AUC(0-t_{LAST}) + $C(t_{LAST})$ / KEL. The 90% confidence intervals (CI) from the Two One-Sided Tests Procedure were calculated for AUC, AUCINF, and CMAX.

VIII. Results

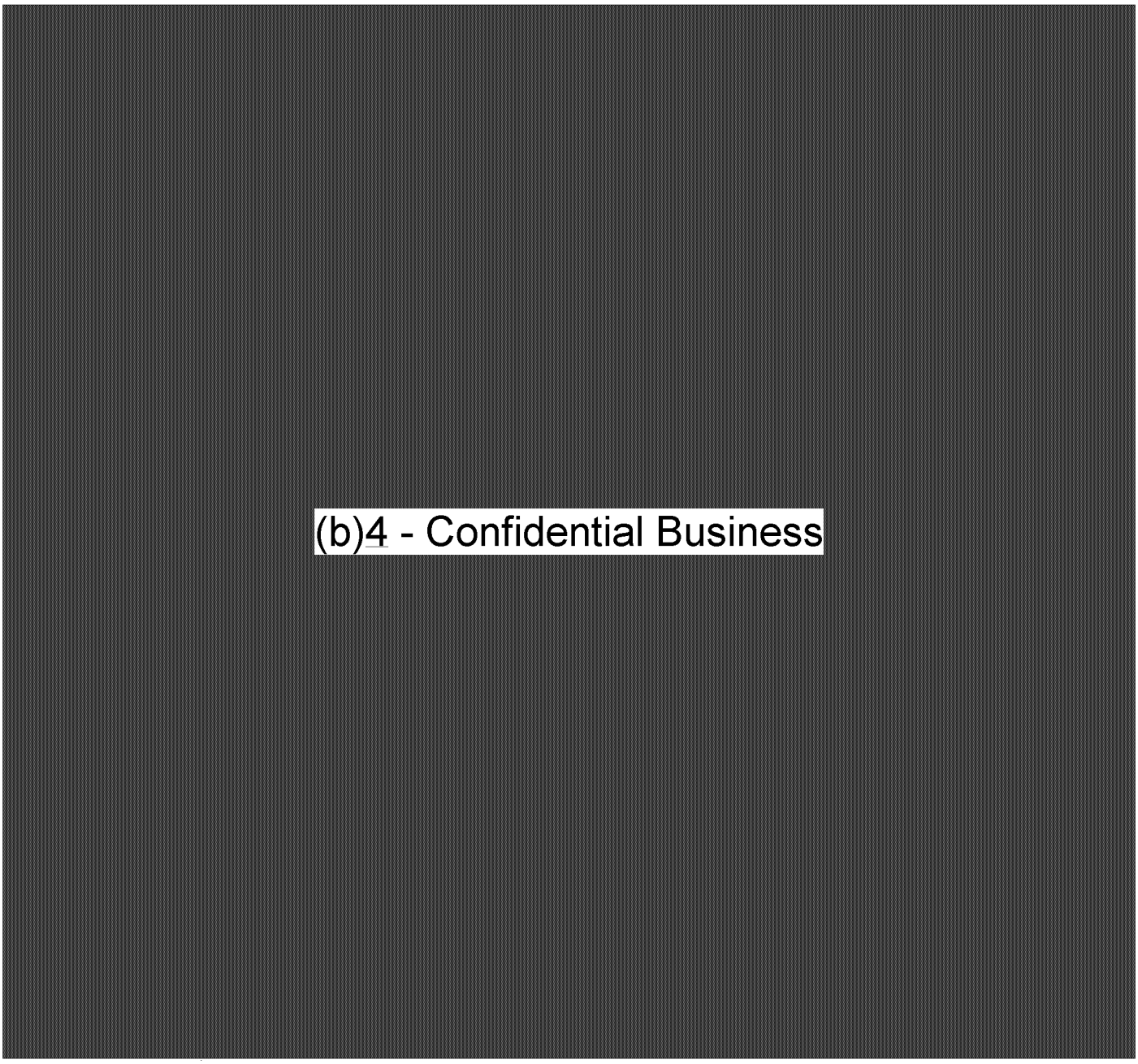
A. Completion: Of the 26 subjects enrolled, 25 subjects completed both study phases. Subject 13 withdrew for personal reasons after Period 1. Data was analyzed and reported for 24 subjects (first 12 subjects to complete from each dosing sequence).

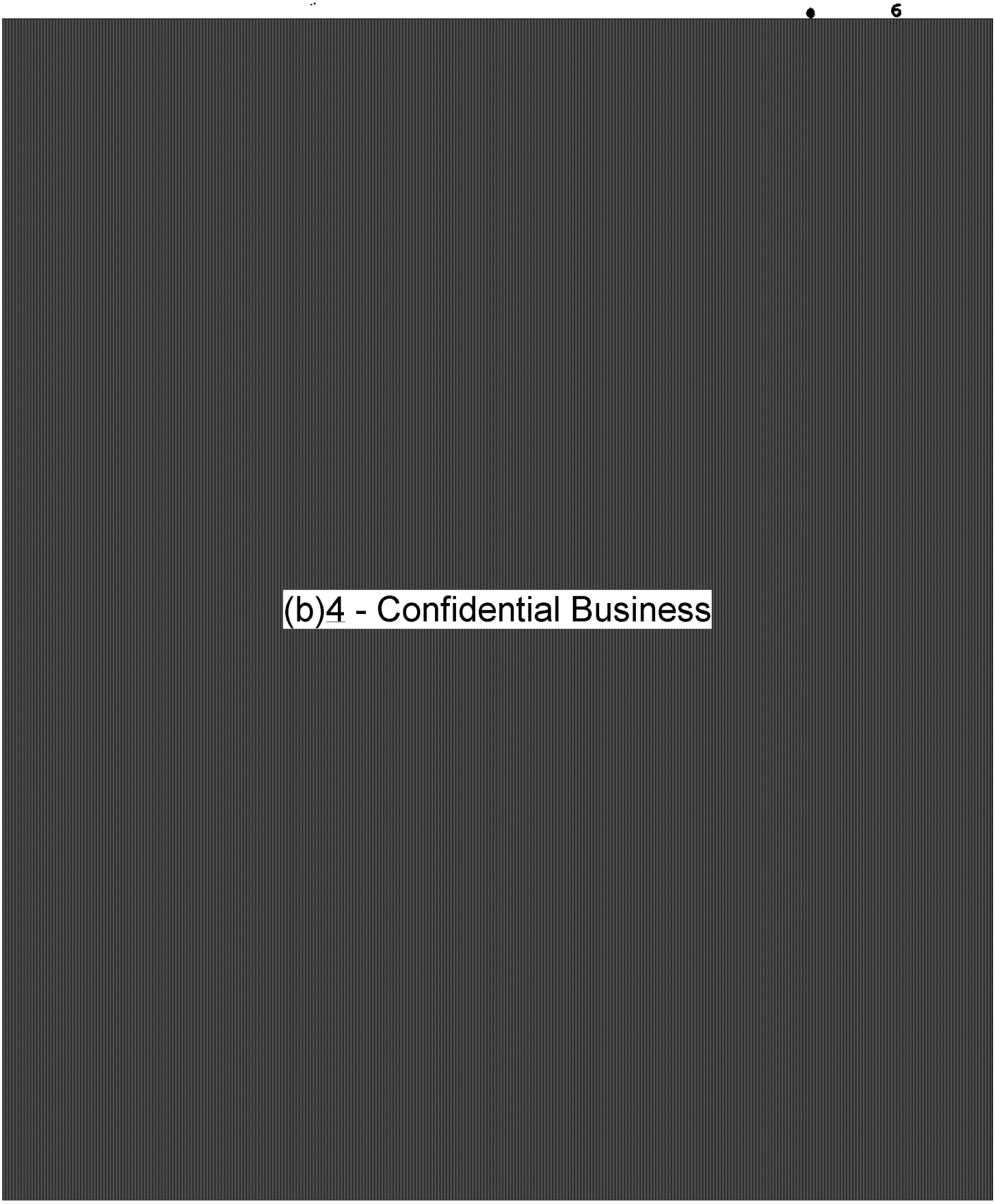
B. Formulation: Comparative formulations of the test products atenolol/chlorthalidone 100/25 mg tablet and 50/25 mg tablet are shown in Attachment 1.

C. Dissolution: The results of dissolution testing for both strengths of the test product are shown in Table 1 (attached).

D. Adverse Events: Clinical complaints are summarized in Attachment 2. No medication was required in any case.

E. Analytical:

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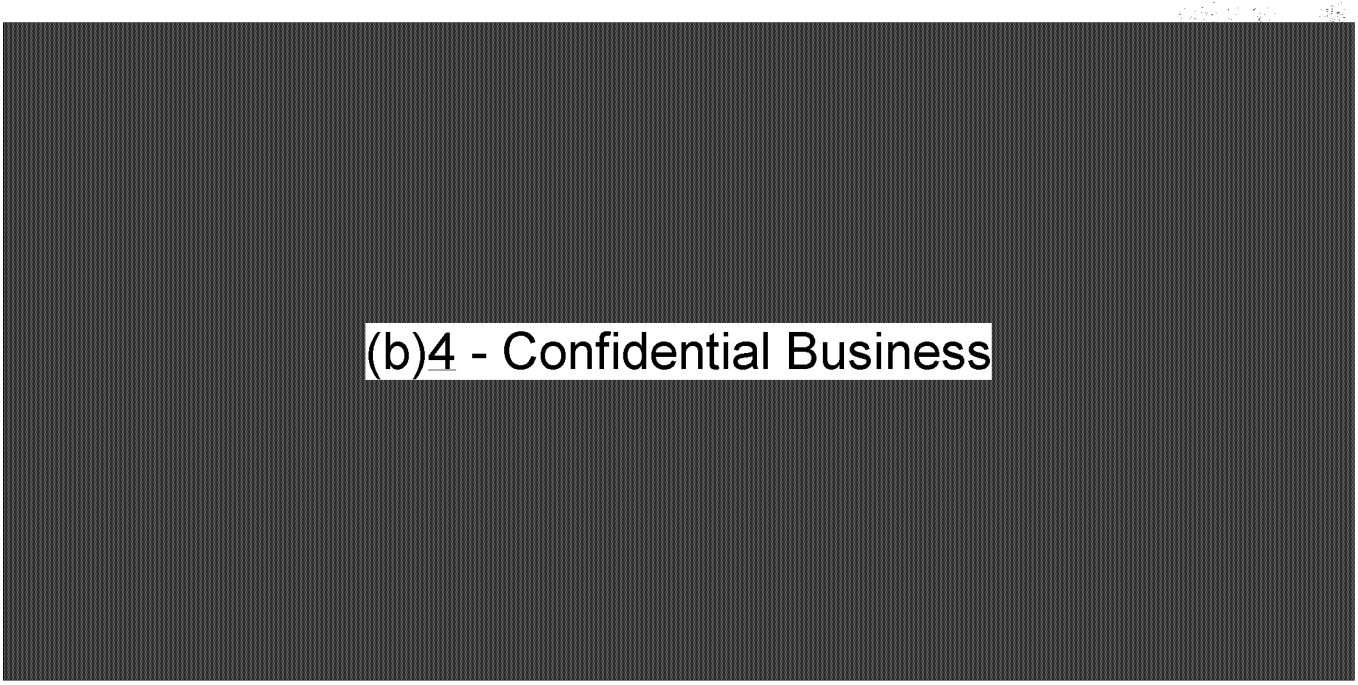

F. Pharmacokinetics/Statistics

Table 4 (attached) - Mean blood levels of atenolol as reported by the sponsor

Table 5 (attached) - Mean pharmacokinetic parameters of atenolol as reported by the sponsor

Table 6 (attached) - Mean blood levels of chlorthalidone as reported by the sponsor

Table 7 (attached) - Mean pharmacokinetic parameters of chlorthalidone as reported by the sponsor

IX. Comments

A. Test Product Information:

1. The sponsor has not stated either the theoretical or finished batch sizes for the biostudy batch of test product.

2. The sponsor has not stated the potency of either the test or reference biostudy products.

3. The dissolution testing (Table 1 attached) is acceptable. The sponsor has stated incorrectly the specification for atenolol as NLT (b)4 45 min, while the Division specification is NLT (b)4 / 30 min. The sponsor stated (b)4 as the analytical method, but provided no other details.

B. Analytical

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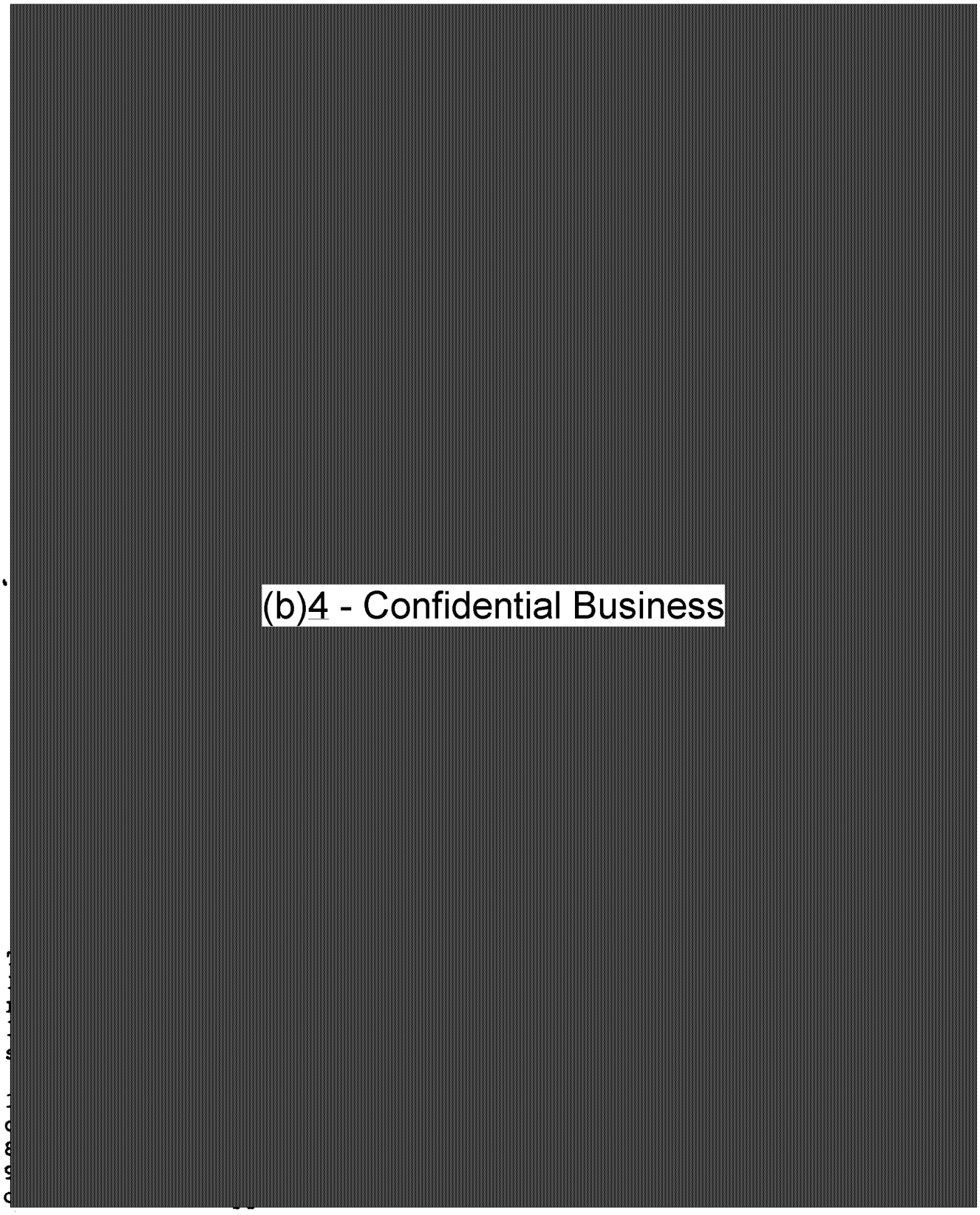
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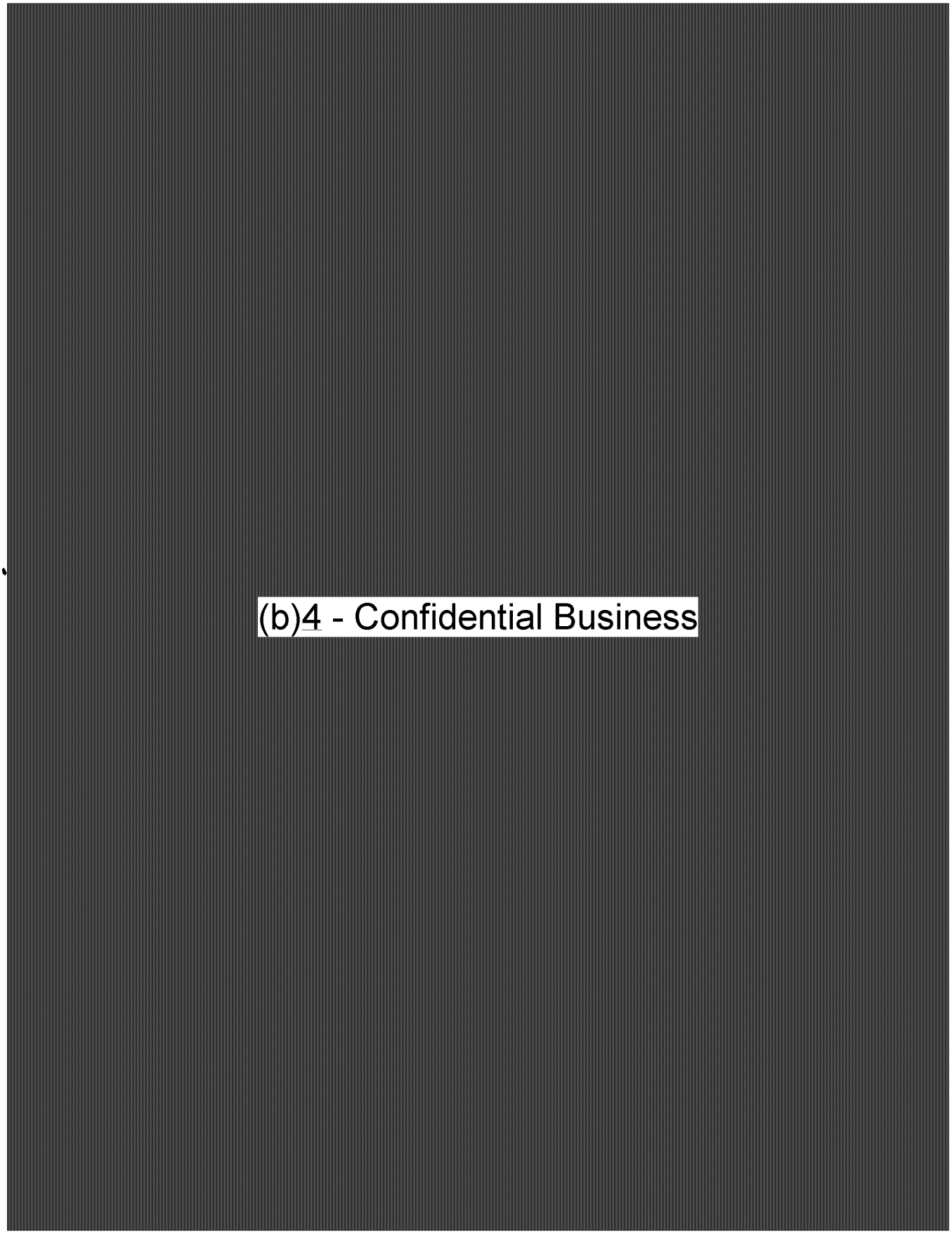
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C. Pharmacokinetics/Statistics

14. Mean blood levels of atenolol resulting from both treatments as reported by the sponsor are shown in Table 4 (attached). At all times except 0.5 and 36 hr, mean blood atenolol levels from Trt. B exceeded mean levels from Trt. A (B>A), with differences of -2.6 to -16.4%. There were statistically significant ($p < 0.05$) treatment effects at 1.5, 2.5, 3, 4, 6, 8, and 10 hr postdose, and a significant ($p < 0.05$) period effect at 18 hr. There were no nonzero predose atenolol blood levels with missing values for S24.

15. Mean pharmacokinetic parameters of atenolol resulting from both treatments as reported by the sponsor are shown in Table 5